DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Los Angeles District 94586

19701 Fairchild
Irvine, California 92612-2506
Telephone (949) 608-2900

WARNING LETTER

Certified Mail
Return Receipt Requested

March 11, 2004

Mr. Mark Johnson
Tissue Processing Group Manager
American Red Cross Transplantation Services
3535 Hyland Ave.
Costa Mesa, CA 92626

W/L 32-04

Dear Mr. Johnson:

During an inspection of your firm located at 3535 Hyland Ave, Costa Mesa, CA 92626, conducted between October 20 and November 25, 2003, our investigators determined that your firm manufactures and distributes cryopreserved heart valves, which are regulated as devices, and human tissues for transplantation, which are regulated as tissues under 21 CFR Part 1270 and section 361 of the Public Health Service Act.

With regard to the cryopreserved human heart valve allograft, this product is a device as defined by section 201 (h) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act). Our investigators documented significant deviations from the Quality System Regulations (QSR), as set forth in Title 21 Code of Federal Regulations (21 CFR), Part 820. These deviations cause your devices to be adulterated within the meaning of Section 501 (h) of the Act. These deviations include:

1. Failure of management to fully implement and maintain an adequate and effective Quality System and Quality Policy at all levels of the organization. For example:

   - Employee training files lack documented training on the organization's Quality Policy. You indicated that the policy is considered to be for 'information purposes only' and therefore documentation of employee training is not required. However, the regulation expressly requires that management with executive responsibility shall ensure that the Quality Policy is understood, implemented, and maintained at all levels of the organization. Since the Quality Policy is required to be understood by all, documentation of training is required. [21 CFR 820.20 (a) & 820.25 (b)]

- Training in the Quality System Regulations has not been administered to employees in critical management and production positions where knowledge of the Quality System Regulations is necessary to assure that those employees perform their activities correctly. [21 CFR 820.25 (a) & (b)]

- Your establishment's procedures governing management's review of the suitability and effectiveness of the Quality System do not identify the information management must consider as part of its periodic review. [21 CFR 820.20 (c) & 820.100 (a) (7)]

2. Failure to establish and maintain a design history file for your human heart valve allograft device, a class III device, containing or referencing the records necessary to demonstrate that the design was developed in accordance with the approved design plan and the requirements of this part. [21 CFR 820.30(j)] For example:

   - You have not performed a risk analysis for risks and hazards associated with the human heart valve allograft device. For example, after multiple complaints associated with heart allograft wall fractures were reported to your company, your investigation revealed that the allograft fractures were due to thermal shock fracturing. As a result, you developed new thawing and dilution procedures and changed the labeling. However, no risk analysis was performed. [21 CFR 820.30 (c) (d) & (g)]

   - You did not follow procedures for the identification, documentation, validation, verification, review and approval of design changes when you made design changes to the thaw and dilution design of the device to prevent thermal shock fracturing. For example, there was no documentation describing the results of the design effort at each design phase. Additionally, there was no documented, comprehensive, systematic examination to evaluate adequacy of the design requirements and to identify problems. [21 CFR 820.30(i)]

   - You did not perform adequate design validation of the device, to ensure that the device conformed to defined user needs and intended uses, in that you have not performed stability studies to support the shelf life of the device. [21 CFR 820.30(g)]

3. You failed to ensure that device packaging and shipping containers are designed and constructed to protect the device from alteration or damage during the customary conditions of processing, storage, handling, and distribution. For example: You performed packaging validation using empty pouches, which did not adequately simulate the customary conditions of processing, storage, handling, and distribution. [21 CFR 820.130]

4. Failure to perform adequate process validation with a high degree of assurance. [21 CFR 820.75(a)] For example:

   - The antibiotic disinfection process validation approved 9/25/93, Antibiotic Challenge, was not adequate. A worst case multiple microbe challenge was not performed, organisms were individually tested in the disinfection solution. A two log reduction

was not achieved for Candida albicans. Additionally, the rationale for the organisms selected for the study could not be explained. [21 CFR 820.75 (a)]

- The antibiotic disinfection process validation dated 3/12/98, Time Kill Test Assay for Antimicrobial Agents, was not adequate. The rationale for the organisms selected for the study could not be explained and were not the same organisms as those selected in the Antibiotic Challenge. Yeasts and molds were excluded. A worst case multiple microbe challenge was not performed, organisms were individually tested. Actual heart valves or simulated product was not used, blended myocardium tissue prepared by a non-validated grinding method were used. Results did not show a two log reduction. [21 CFR 820.75 (a)]

- The cryopreservation process dated 5/19/95, Computer Rate Controlled Freezer for Cryopreservation of Human Tissue, was not adequate. The validation included determining the maximum tolerance limits of the cryopreservation unit to freeze heart valves at a specified rate but only cryopreservation solution was used, not heart valves or a simulated product. [21 CFR 820.75 (a)]

- The cleaning validation performed for the Class 100 processing rooms was not adequate. Results did not support that the cleaning activities were effective. [21 CFR 820.75 (a) & 820.70 (e)]

- The packaging validation was not performed according to the approved protocol that required use of heart valves or simulated product to be included in the sealed pouches. Pouches were empty. [21 CFR 820.30 (g) & 820.75 (a)]

5. Failure to establish a Device Master Record in that the Device Master Record does not contain or refer to the location of device specifications and packaging and labeling specifications. [21 CFR 820.181 (a) & (d)]

6. Failure to establish and maintain procedures to ensure that all purchased or otherwise received product and services conform to specified requirements. [21 CFR 820.50] For example:

   - You did not evaluate the ability of your suppliers of antibiotics, inner and outer cryopreservation package materials, and biological indicators to provide you with materials that meet your specified requirements. Furthermore, these suppliers are included on your approved supplier list without being audited, scheduled for audit or other documentation to support the ability of these suppliers to provide you with materials that meet your specifications. Your statement that you considered these suppliers to be "grandfathered" is without support in the rule, which applies to all suppliers. [21 CFR 820.50(a)]

7. Failure to establish and maintain procedures for acceptance of incoming product. Incoming product shall be inspected, tested, or otherwise verified as conforming to

specified requirements. Acceptance or rejection shall be documented. [21 CFR 820.80(b)] For example:

- You accepted sterile media ([redacted]), used for tissue transport after procurement, as a component of the disinfection solution formula, and as a component of the cryopreservation solution formula, on the basis of a certificate of analysis and visual check. You have not verified that the product conforms to the certificate of analysis and package insert to assure that the [redacted] meets incoming product specifications, such as sterility so that it does not add contamination to the product during processing. For example, the [redacted] is received with a Certificate of Analysis and no periodic testing is done to verify that the product conforms to the COA or package inserts. [21 CFR 820.80 (b)]

- You accepted antibiotics used in the disinfection process without a certificate of analysis and performed no further testing to assure conformance with incoming product specifications. [21 CFR 820.80(b)]

Our investigators also determined that your firm processes human tissue intended for transplantation. Our investigators documented significant violations of the requirements for human tissue intended for transplantation set forth in Title 21, Code of Federal Regulations (21 CFR), Part 1270, promulgated under the authority of Section 361 of the Public Heath Service Act. These violations include:

Failure to prepare, validate, and follow written procedures for prevention of infectious disease contamination and cross-contamination during processing, as required by 21 CFR 1270.31(d). For example:

1. Written procedures were not validated in that:

   - Your October 1999 validation of the antibiotic disinfection process was not based on the manufacturing process actually used, in that the procedure used during validation required shaking of the sample and antibiotic solution test mixture, while standard operating procedure (SOP) TSP E1.073v1, entitled "Processing Skin for Cryopreservation", which is used during manufacturing, does not require shaking of the skin tissue and antibiotic solution mixture; deionized water was used in the dilution of the antibiotic solution for the validation study, while the antibiotic solution used in manufacturing is diluted with [redacted] nutrient media; and a stronger concentration of antibiotics was used in the disinfection formula during validation than is used during manufacturing.

   - Validation of your manufacturing process did not include a worst case multiple microbe challenge. Your validation process was limited to individual testing of microorganisms in the disinfection solution. Your validation efforts do not support your manufacturing process when multiple microorganisms may be present on procured tissue.

- The validation performed does not address the risk that the antibiotic disinfection solution may interfere with or inhibit the growth of microorganisms in culture media during post-processing culturing of antibiotic-treated tissues.

- Your firm has not assured that the microbiology testing methods were validated to ensure that residual antibiotic/antifungal disinfection solution or other processing solutions do not inhibit the growth of microorganisms resulting in false-negative microbiological testing results. Furthermore, your firm has not determined the effect of the shipping method on tissue samples for culture. In addition, there is no data to demonstrate the effect that the shipping method has on tissue samples.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence to each requirement of the FD&C Act, Section 361 of the Public Health Service Act, and the federal regulations. The specific violations noted in this letter and in the Form FDA-483, Inspectional Observations issued and discussed on November 25, 2003, at the closeout of the inspection, may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. You are responsible for investigating and determining causes of the violations identified by the FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

We acknowledge receipt of your February 25, 2004, response to the FDA-483 observations. We find your response to be inadequate. For example, we find that your implementation steps for QSR is inadequate and the timeframes to be unrealistic. Your response also did not adequately address the frequency issue of Management Review of Quality Systems. Each of your corrective actions should address system level improvements. It will not be necessary to resubmit any documents previously submitted if they are applicable to the issues in this letter. Please reference applicable documents already submitted in your response to this letter.

Federal agencies are advised of the issuance of all warning letters pertaining to medical devices so that they may take this information into account when considering the award of contracts. Additionally, no premarket applications for a device to which the Quality System/Good Manufacturing Practice (GMP) deficiencies are reasonably related will be approved until the device violations described above have been corrected. Also, no requests for Certificates to Foreign Governments will be granted until the violations related to the subject devices have been corrected.

You should take prompt action to correct these deviations. Failure to do so may result in regulatory action being initiated by FDA, including, but not limited to, seizure, injunction, civil penalties, and/or Order for Retention, Recall and/or Destruction.

You should notify this office within fifteen (15) working days of receipt of this letter of the specific steps you have taken to correct the noted violations including an explanation of each step being taken to identify and prevent the recurrence of similar violations. If corrective action cannot be completed within (15) working days, state the reason for the delay and the time within which the corrections will be completed.

If you have any questions regarding this letter, please contact Ms. MaryLynn Datoc, Compliance Officer at 949-608-4428. Your written reply should be addressed to:

Director of Compliance
U. S. Food and Drug Administration
19900 MacArthur Blvd, Suite 300
Irvine, CA 92612

Sincerely,

Alonza E. Cruse
District Director